A Human Pleiotropic Multiorgan Condition Caused by Deficient Wnt Secretion.

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Public Summary:
BACKGROUND: Structural birth defects occur in approximately 3% of live births; most such defects lack defined genetic or environmental causes. Despite advances in surgical approaches, pharmacologic prevention remains largely out of reach. METHODS: We queried worldwide databases of 20,248 families that included children with neurodevelopmental disorders and that were enriched for parental consanguinity. Approximately one third of affected children in these families presented with structural birth defects or microcephaly. We performed exome or genome sequencing of samples obtained from the children, their parents, or both to identify genes with biallelic pathogenic or likely pathogenic mutations present in more than one family. After identifying disease-causing variants, we generated two mouse models, each with a pathogenic variant "knocked in," to study mechanisms and test candidate treatments. We administered a small-molecule Wnt agonist to pregnant animals and assessed their offspring. RESULTS: We identified homozygous mutations in WLS, which encodes the Wnt ligand secretion mediator (also known as Wntless or WLS) in 10 affected persons from 5 unrelated families. (The Wnt ligand secretion mediator is essential for the secretion of all Wnt proteins.) Patients had multiorgan defects, including microcephaly and facial dysmorphism as well as foot syndactyly, renal agenesis, alopecia, iris coloboma, and heart defects. The mutations affected WLS protein stability and Wnt signaling. Knock-in mice showed tissue and cell vulnerability consistent with Wnt-signaling intensity and individual and collective functions of Wnts in embryogenesis. Administration of a pharmacologic Wnt agonist partially restored embryonic development. CONCLUSIONS: Genetic variations affecting a central Wnt regulator caused syndromic structural birth defects. Results from mouse models suggest that what we have named Zaki syndrome is a potentially preventable disorder. (Funded by the National Institutes of Health and others.).

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